PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 9/48, 9/107, 47/10, 47/26, 47/44, A61P 3/04

A1

(11) International Publication Number: WO 00/57859

(43) International Publication Date: 5 October 2000 (05.10.00)

(21) International Application Number: PCT/US00/07650

(22) International Filing Date: 23 March 2000 (23.03.00)

(30) Priority Data:
09/282,513 31 March 1999 (31.03.99) US

(71) Applicant: ABBOTT LABORATORIES [US/US]; D377/AP6D, 100 Abbott Park Road, Abbott Park, IL 60064–6050 (US).

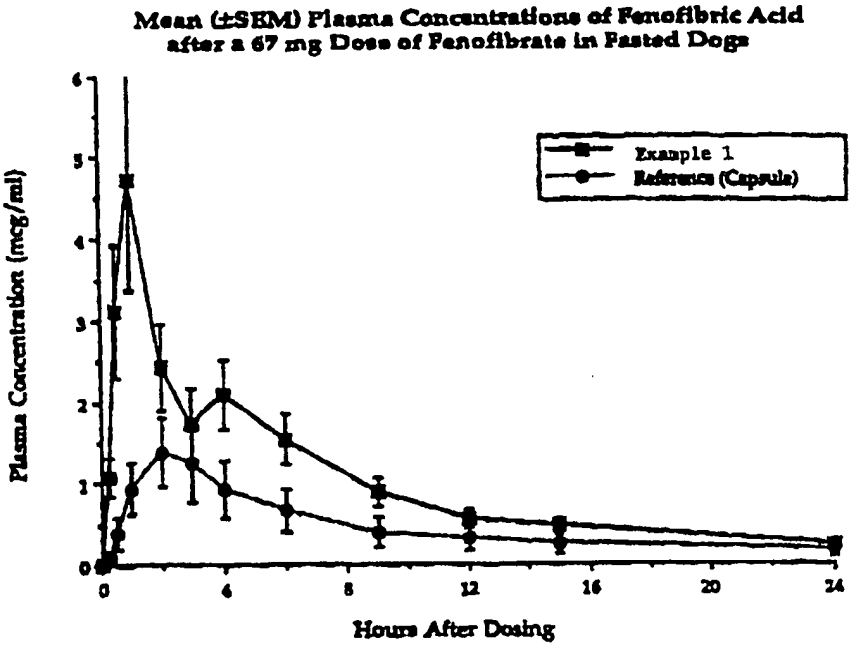
(72) Inventors: PATEL, Jitendra, P.; 1105 Ashbury Lane, Libertyville, IL 60048 (US). SANZGIRI, Yeshwant, D.; 1323 Deer Run, Gurnee, IL 60031 (US). LIPARI, John, M.; 6600 Apollo Drive, Racine, WI 53406 (US). REILAND, Thomas, L.; 33974 North Lake Shore Drive, Gages Lake, IL 60030 (US).

(74) Agents: SICKERT, Dugal, S. et al.; D377/AP6D, 100 Abbott Park Road, Abbott Park, IL 60064–6050 (US).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL FORMULATIONS COMPRISING LIPID–REGULATING AGENTS



(57) Abstract

The present invention is directed to a formulation comprising a lipid–regulating agent dissolved or dispersed in at least one oil and an emulsifier or emulsifier blend, the resulting mixture being capable of forming an emulsion upon dilution in an aqueous medium.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Novel Formulations Comprising Lipid-Regulating Agents

Field of the Invention

The present invention relates to novel formulations comprising lipid-regulating agents.

Background of the Invention

2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethylester, also known as fenofibrate, is representative of a broad class of compounds having pharmaceutical utility as lipid regulating agents. More specifically, this compound is part of a lipid-regulating agent class of compounds commonly known as fibrates, and is disclosed in U.S. Patent No. 4,058,552.

Fenofibrate has been prepared in several different formulations, c.f., U.S. Patent No. 4,800,079 and U.S. Patent No. 4,895,726. U.S. Patent No. 4,895,726 discloses a co-micronized formulation of fenofibrate and a solid surfactant.

U.S. Patent No. 4,961,890 discloses a process for preparing a controlled release formulation containing fenofibrate in an intermediate layer in the form of crystalline microparticles included within pores of an inert matrix. The formulation is prepared by a process involving the sequential steps of dampening said inert core with a solution based on said binder, then projecting said fenofibrate microparticles in a single layer onto said dampened core, and thereafter drying, before said solution based on said binder dissolves said fenofibrate microparticles, and repeating said three steps in sequence until said intermediate layer is formed.

European Patent Application No. EP0793958A2 discloses a process for producing a fenofibrate solid dosage form utilizing fenofibrate, a surface active agent and polyvinyl pyrrolidone in which the fenofibrate particles are mixed with a polyvinyl pyrrolidone solution. The thus obtained mixture is granulated with an aqueous solution of one or more surface active agents, and the granulate thus produced is dried.

PCT Publication No. WO 82/01649 discloses a fenofibrate formulation having granules that are comprised of a neutral core that is a mixture of saccharose and starch. The neutral core is covered with a first layer of fenofibrate, admixed with an excipient and with a second microporous outer layer of an edible polymer.

U.S. Patent No. 5,645,856 describes the use of a carrier for hydrophobic drugs, including fenofibrate, and pharmaceutical compositions based thereon. The carrier comprises a digestible oil and a pharmaceutically-acceptable surfactant component for dispersing the oil in vivo upon administration of the carrier, which comprises a hydrophilic surfactant, said surfactant component being such as not to substantially inhibit the in vivo lipolysis of the digestible oil.

Gemfibrozil is another member of the fibrate class of lipid-regulating agents. U.S. Patent No. 4,927,639 discloses a disintegratable formulation of gemfibrozil providing both immediate and sustained release, comprising a tablet compressed from a mixture of a first and second granulation, and a disintegration excipient operable to effect partial or complete disintegration in the stomach. The first granulation comprises finely divided particles of pure gemfibrozil granulated with at least one cellulose derivative, and the second granulation comprises finely divided particles of pure gemfibrozil granulated with a pharmaceutically-acceptable water soluble or insoluble

polymer which are then uniformly coated with a pharmaceutically-acceptable (meth)acrylate copolymer prior to admixture with the first granulation. The first and second granulations are present in the final composition in a ratio of from about 10:1 to about 1:10.

U.S. Patent 4,925,676 discloses a disintegratable gemfibrozil tablet providing both immediate and enteric release, which is compressed from a mixture of a first granulation of gemfibrozil with at least one acid-disintegratable binder, and a second granulation formed from the first granulation, but regranulated or coated with an alkali-disintegratable formulation of at least one substantially alkali-soluble and substantially acid-insoluble polymer.

Another class of lipid-regulating agents are commonly known as statins, of which pravastatin and atorvastatin are members. U.S. Patents 5,030,447 and 5,180,589 describe stable pharmaceutical compositions, which when dispersed in water have a pH of at least 9, and include a medicament which is sensitive to a low pH environment, such as pravastatin, one or more fillers such as lactose and/or microcrystalline cellulose, one or more binders, such as microcrystalline cellulose (dry binder) or polyvinylpyrrolidone (wet binder), one or more disintegrating agents such as croscarmellose sodium, one or more lubricants such as magnesium stearate and one or more basifying agents such as magnesium oxide.

It is an object of the present invention to provide formulations of lipid-regulating agents having enhanced bioavailability and longer half-life when compared to commercially available formulations.

Summary of the Invention

The present invention is directed to a formulation comprising a lipid-regulating agent dissolved in an oil, with subsequent emulsification using one or more emulsifiers. This formulation forms fine and stable emulsions. The emulsions result in an increase in drug solubility, oral bioavailability and half-life.

The formulation may be administered directly, diluted into an appropriate vehicle for administration, encapsulated into soft or hard gelatin shells or capsules for administration, or administered by other means obvious to those skilled in the art.

Brief Description of the Drawings

Figure 1 is a graph showing the plasma concentration in fasted dogs of the formulation of Example 1 and a reference compound.

Detailed Description of the Invention

The bulk lipid-regulating agent may be prepared by any available method, as for example the compound fenofibrate may be prepared by the procedure disclosed in U.S. Patent No. 4,058,552, or the procedure disclosed in U.S. Patent No. 4,739,101, both herein incorporated by reference.

The solution comprising the lipid-regulating agent is prepared by dissolving said agent in the oil with adequate mixing. An emulsifier or emulsifier blend is added to said mixture and mixed until uniform. If desired, water can be

then added to the resulting mixture with agitation to form a uniform emulsion.

The delivery system of the present invention results in increased solubility, half-life and bioavailability of the lipid-regulating agent. It can be further diluted with additional liquids or it may be thickened and/or stabilized with various pharmaceutical excipients to vary its existing properties.

Suitable oils include, but are not limited to, any pharmaceutically acceptable oil, such as, for example, soybean oil, coconut oil, canola oil, corn oil, palm kernel oil, cottonseed oil, olive oil, peanut oil, safflower oil and sesame oil.

Suitable emulsifiers include any pharmaceutically acceptable hydrophilic or lipophilic emulsifier or combinations thereof, such as, for example, phospholipids, polyoxyethylene sorbitan fatty acid derivatives, sorbitan fatty acid derivatives, polyoxyl-35-castor oil (Cremophor EL, available from BASF), castor oil or hydrogenated castor oil ethoxylates, polyglycerol esters of fatty acids, fatty acid ethoxylates, alcohol ethoxylates, polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, and TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate). Preferred emulsifiers include polyoxyethylene sorbitan fatty acid derivatives, sorbitan fatty acid derivatives and polyoxyl-35-castor oil (Cremophor EL, available from BASF).

Other optional ingredients which may be included in the compositions of the present invention are those which are conventionally used in oil-based drug delivery systems, e.g. antioxidants such as, for example, tocopherol, ascorbyl palmitate, ascorbic acid, butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, etc.; pH stabilizers such as, for example, citric acid, tartaric

acid, fumaric acid, acetic acid, glycine, arginine, lysine, potassium hydrogen phosphate, etc.; thickeners/suspending agents such as, for example, hydrogenated vegetable oils, beeswax, colloidal silicon dioxide, gums, celluloses, silicates, bentonite, etc.; flavoring agents such as, for example, cherry, lemon, aniseed flavors, etc.; sweeteners such as, for example, aspartame, saccharin, cyclamates, etc.; and co-solvents, such as, for example, ethanol, propylene glycol, polyethylene glycol, dimethyl isosorbide, etc.

The resulting liquid comprising the lipid-regulating agent may be dosed directly for oral administration, diluted into an appropriate vehicle for oral administration, filled into soft or hard shells or capsules for oral administration, or delivered by some other means obvious to those skilled in the art. The said liquid can be used to improve the oral bioavailability, and increase the half-life and solubility of said lipid-regulating agent.

The invention will be understood more clearly from the following non-limiting representative examples:

Example 1

SR Soybean oil (24.33 g) was added to a beaker and fenofibrate (0.67 g) was dissolved in it by stirring. Sorbitan monooleate (2.5 g) was added to the beaker and mixed until uniform. Polysorbate 80 (0.5 g) was then added and mixed until uniform. Finally water (72 g) was added slowly with constant mixing until a uniform emulsion resulted.

Example 2

SR Soybean oil (24 g) is added to a beaker and pravastatin (1 g) is dispersed in it by stirring. Sorbitan monooleate (2.5 g) is added to the beaker and mixed until uniform. Polysorbate 80 (0.5 g) is then added and mixed until uniform. Finally water (72 g) is added slowly with constant mixing until a uniform emulsion resulted.

Example 3

SR Soybean oil (24 g) is added to a beaker and atorvastatin (1 g) is dispersed in it by stirring. Sorbitan monooleate (2.5 g) is added to the beaker and mixed until uniform. Polysorbate 80 (0.5 g) is then added and mixed until uniform. Finally water (72 g) is added slowly with constant mixing until a uniform emulsion resulted.

Example 4

The emulsion prepared by the process described in Example 1, and from a commercial fenofibrate composition, Lipanthyl 67M (Groupe Fournier) (Reference), were administered to a group of dogs at a dose of 67 mg fenofibrate/dog (10 mL emulsion or one capsule/dog). The plasma concentrations of fenofibric acid were determined by HPLC. Concentrations were normalized to a 6.7 mg/kg dose in each dog. Figure 1 presents the resulting data in graph form. The results provided as mean ± SD, n=6, were as follows:

Lipanthyl 67M (Reference):

Cmax = 1.88 ± 0.97 mcg/ml

Tmax = 1.6 ± 0.9 hr

$t_{1/2}$ = 4.5 hr

AUC (0-24) = 11.08 ± 9.42 mcg•hr/ml

Emulsion of Example 1:

Cmax = 4.97 ± 3.13 mcg/ml

Tmax = 1.1 ± 0.5 hr

$t_{1/2}$ = 7.8 hr

AUC (0-24) = 24.21 ± 11.69 mcg•hr/ml

AUC relative to Reference = 2.2

Claims

1. A composition comprising a lipid-regulating agent dissolved or dispersed in at least one oil with one or more emulsifiers, wherein the mixture is capable of forming an emulsion upon dilution with an aqueous phase.

2. A composition of claim 1 wherein said lipid-regulating agent is a fibrate.

3. A composition of claim 2 wherein said fibrate is fenofibrate.

4. A composition of claim 1 wherein said lipid-regulating agent is a statin.

5. A composition of claim 4 wherein said statin is pravastatin.

6. A composition of claim 4 wherein said statin is atorvastatin.

7. A composition of claim 1 wherein at least one or more of said emulsifiers is selected from phospholipids, polyoxyethylene sorbitan fatty acid derivatives, sorbitan fatty acid derivatives, Polyoxyl-35-castor oil (Cremophor EL, available from BASF), castor oil or hydrogenated castor oil ethoxylates, polyglycerol esters of fatty acids, fatty acid ethoxylates, alcohol ethoxylates, polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, and TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate).

8. A composition of claim 7 wherein at least one or more of said emulsifiers is polyoxyethylene sorbitan fatty

acid derivatives, sorbitan fatty acid derivatives and polyoxyl-35-castor oil.

9. A composition of claim 1 wherein said oil is selected from soybean oil, coconut oil, canola oil, corn oil, palm kernel oil, cottonseed oil, olive oil, peanut oil, safflower oil and sesame oil.

10. A composition of claim 9 wherein said oil is soybean oil.

11. A composition of claim 1 further comprising a co-solvent.

12. A composition of claim 11 wherein said co-solvent is ethanol, propylene glycol or polyethylene glycol.

13. A delivery system comprising a composition of claim 1.

14. A delivery system of claim 13 wherein said delivery system is an emulsion.

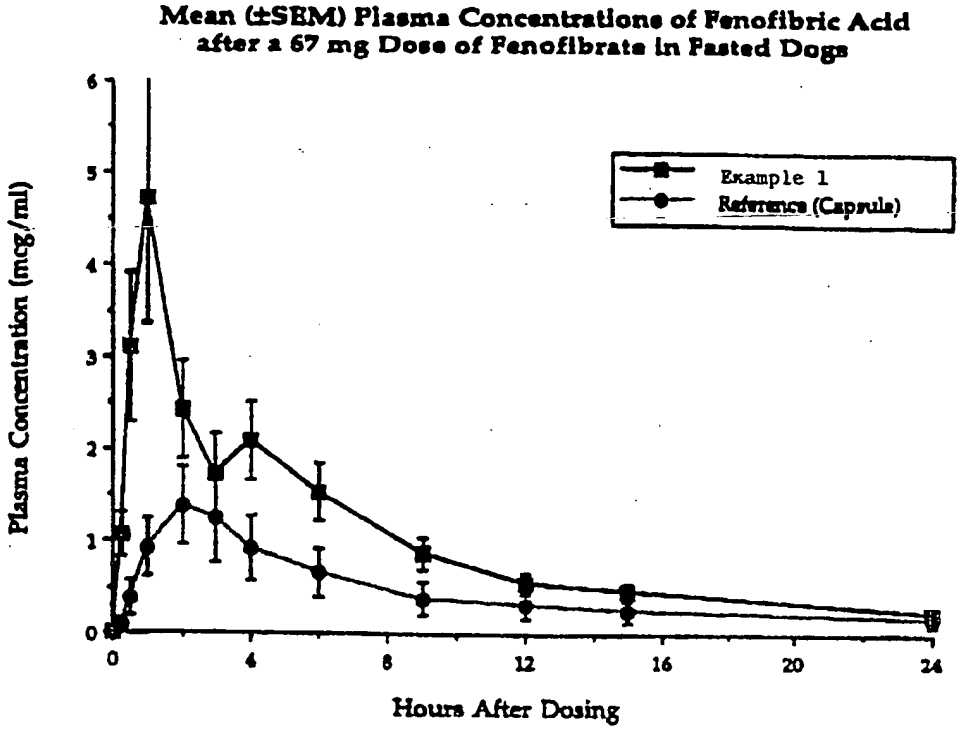
15. A delivery system of claim 13 wherein said delivery system is a capsule.

16. A method of treating hyperlipidemia comprising the administration of a composition of claim 1 to a patient.

17. A method of treating hyperlipidemia comprising the administration of a composition of claim 3 to a patient.

18. A method of treating hyperlipidemia comprising the administration of a composition of claim 14 to a patient.

FIGURE 1


Mean (±SEM) Plasma Concentrations of Fenofibric Acid
after a 67 mg Dose of Fenofibrate in Fasted Dogs
Example 1
Reference (Capsule)
Plasma Concentration (mcg/ml)
Hours After Dosing
0
1
2
3
4
5
6
0
4
8
12
16
20
24

INTERNATIONAL SEARCH REPORT

Inte: onal Application No
PCT/US 00/07650

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/48 A61K9/107 A61K47/10 A61K47/26 A61K47/44
A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 645 856 A (LACY JONATHAN ERNEST ET AL) 8 July 1997 (1997-07-08) cited in the application column 1, line 4 - line 7 column 3, line 56 -column 4, line 14 column 4, line 36 -column 5, line 51 column 6, line 34 -column 7, line 55 column 8, line 45 -column 9, line 14 column 12, line 22 - line 23 column 12, line 54 -column 13, line 7 column 13, line 47 - line 57; claims 1-8,15-17; example 6 --- -/--	1-3, 7-10,15, 18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2000	11/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Marttin, E

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 00/07650

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 031 603 A (AMERICAN CYANAMID CO) 8 July 1981 (1981-07-08) page 1, line 4 - line 19 page 3, line 9 - line 17 page 4, line 12 - line 22 page 4, line 33 -page 5, line 2 page 5, line 26 - line 30; claims 1-8; example 5	1,7,9, 13-18
X	US 4 946 866 A (WOLF HORST ET AL) 7 August 1990 (1990-08-07) column 1, line 36 - line 60 column 2, line 22 - line 43; claims 1,13,14; example 1	1,7, 13-18
X	GB 1 590 864 A (LILLY INDUSTRIES LTD) 10 June 1981 (1981-06-10) page 1, line 41 - line 52 page 2, line 23 - line 63; claims; example 1	1,2, 10-14
A	EP 0 700 678 A (WAKAMOTO PHARMA CO LTD) 13 March 1996 (1996-03-13) page 1, line 3 - line 5 page 4, line 9 - line 13 page 4, line 58 - last line; claims 1,6-9	1,4,5,9, 10,13, 14,16-18
P,X	WO 99 29300 A (MISHRA AWADHESH K ;PARIKH INDU (CA); MOUSSA ISKANDAR (CA); RTP PHA) 17 June 1999 (1999-06-17) page 1, line 1 - line 2 page 5, paragraph 2 -page 8, paragraph 1 page 9, paragraph 2 -page 10, paragraph 1; claims; examples	1-3,7, 11-18

2

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-18 relate to a compound defined by reference to a desirable characteristic or property, namely a "lipid-regulating agent". The term "lipid-regulating agent" as used in the present independent claims 1, 13, 16-18 and in dependent claims 2-12, 14 and 15 defines the active agent by its pharmacological effect. However, a compound canot be sufficiently characterised by its pharmacological effect as it is done by an expression like "lipid-regulating agent", because it is impossible to know which substances are encompassed in this expression. Moreover, a compound cannot be sufficiently characterised by the term "regulating", because this term has no well-recognised meaning and is therefore unclear.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for the concept of "lipid-regulating agent" and those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in claims 2-6.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/US 00/07650

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5645856 A	08-07-1997	AU 686767 B	12-02-1998
		AU 1897495 A	03-10-1995
		CA 2185347 A	21-09-1995
		EP 0750495 A	02-01-1997
		WO 9524893 A	21-09-1995
		JP 10503750 T	07-04-1998
EP 0031603 A	08-07-1981	AU 6501980 A	09-07-1981
		JP 56100718 A	12-08-1981
US 4946866 A	07-08-1990	AT 65398 T	15-08-1991
		DE 3680507 D	29-08-1991
		WO 8700751 A	12-02-1987
		EP 0231367 A	12-08-1987
		JP 2556496 B	20-11-1996
		JP 63500380 T	12-02-1988
GB 1590864 A	10-06-1981	CA 1135623 A	16-11-1982
		DE 2838387 A	31-10-1979
EP 0700678 A	13-03-1996	CA 2153553 A	14-01-1996
		JP 8081360 A	26-03-1996
		US 5693337 A	02-12-1997
WO 9929300 A	17-06-1999	AU 1809499 A	28-06-1999
		AU 1817499 A	28-06-1999
		WO 9929316 A	17-06-1999